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Synthesis of a new fluorinated oxazolidinone and its reactivity as a chiral auxiliary in Aldol reactions

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Abstract

A new enantiomerically pure fluorinated oxazolidinone has been prepared from a fluorinated imidoyl chloride and an optically pure sulfoxide. The diastereoselective reduction of the β-iminosulfoxide thus formed followed by elimination of the sulfoxide and cyclization of the created aminoalcohol furnishes the desired product. The fluorinated oxazolidinone was subsequently used as a chiral auxiliary in Aldol reactions. We also found that the selective formation of the *syn*-Evans and *syn*-non-Evans diastereoisomer can be controlled by adjusting the Lewis acid/base ratio.

Keywords: Oxazolidinone; Asymmetric synthesis; Organofluorinated compounds; Asymmetric Aldol condensation

1. Introduction

One of the major goals of synthetic organic chemistry is the asymmetric synthesis of molecules, especially those with biological activity that render them useful as pharmaceuticals or agrochemicals. To generate the stereogenic centers for such molecules, the use of chiral auxiliaries has proven to be a powerful tool [1]. In fact, asymmetric Aldol reactions in the presence of chiral auxiliaries is one of the most general methods employed in these syntheses since one C–C bond and two stereogenic centers can be formed in a single step. In particular, chiral oxazolidinone-mediated Aldol reactions have received a great amount of attention and have been applied often to the synthesis of chiral compounds, including on a multi-kilogram scale [2,3]. Thus, in an Aldol reaction of *N*-acyloxazolidinones with the formation of two new stereocenters, the formation of up to four diastereoisomers is possible. Using Evans's terminology, these can be dubbed *syn*-Evans, *anti*-Evans, *syn*-non-Evans, and *anti*-non-Evans (Fig. 1).

At the same time, the substitution of hydrogen atoms for fluorine in organic molecules induces tremendous changes in the physico-chemical properties and chemical reactivity of such molecules, thereby affecting their electronic properties [4]. Some examples of the chemical consequences of fluorine substitution have been reported by Haufe and coworkers, who studied the Diels-Alder reactions of fluorinated compounds and found that they displayed a completely different reactivity compared with the corresponding non-fluorinated analogs [5]. In another recent example, which is more related to this paper, Brigaud and coworkers studied the effect of the introduction of a CF_3 group in an oxazolidine ring to be used as a chiral auxiliary in Aldol reactions for the preparation of enantiomerically pure alcohols, aldehydes and carboxylic acids. Thus, the presence of the CF_3 group in 4-phenyl-2-trifluoromethyloxazolidine, which was used as a chiral auxiliary, caused very high diastereoselectivities in amide enolate alkylation reactions, while it also allowed for efficient chiral auxiliary recovery [6]. Finally, Figadère and coworkers reported that the Ti enolate of a chiral α-CF_3 amide [*N*-(3,3,3-trifluoropropionyl)oxazolidine-2-thione] can be efficiently generated and used in Aldol reactions with aliphatic and aromatic aldehydes to yield the *syn*-Evans product with high

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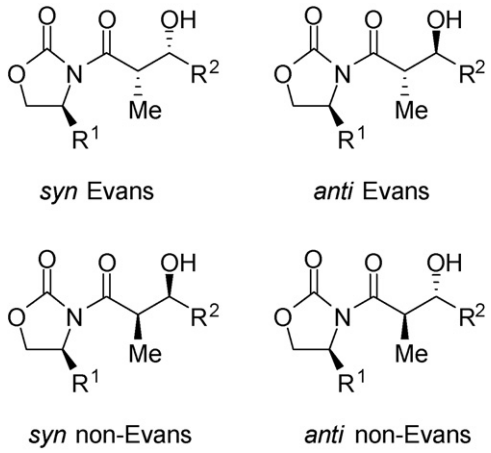
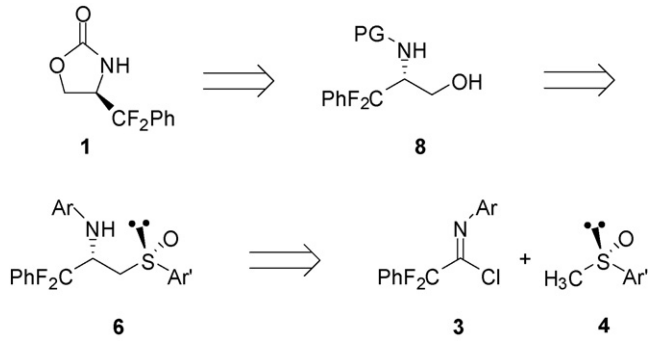


Fig. 1. The four possible diastereomers resulting from the Aldol reaction of an aldehyde and an *N*-propionyl oxazolidinone.

diastereoselectivities [7]. These results clearly show that new fluorinated chiral auxiliaries are appealing synthetic targets. Thus, we decided to prepare a fluorinated oxazolidinone-based structure such as **1** and study the reactivity of its *N*-acyl derivative in asymmetric Aldol reactions.

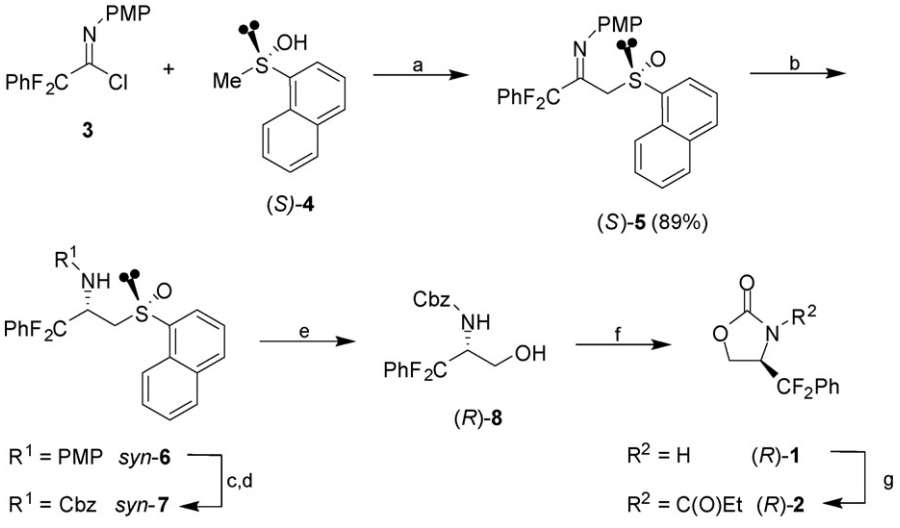
Our retrosynthetic analysis for the synthesis of the fluorinated oxazolidinone **1** is presented in Scheme 1. Formation of a C–C bond was achieved through reaction of imidoyl chloride **3** and (*S*)-methyl-1-naphthylsulfoxide **4**. This reaction was followed by diastereoselective reduction to give β-aminosulfoxide **6**. Elimination of the sulfoxide chiral auxiliary and subsequent cyclization of the aminoalcohol **8** finally afforded the fluorinated oxazolidinone **1**.



Scheme 1.

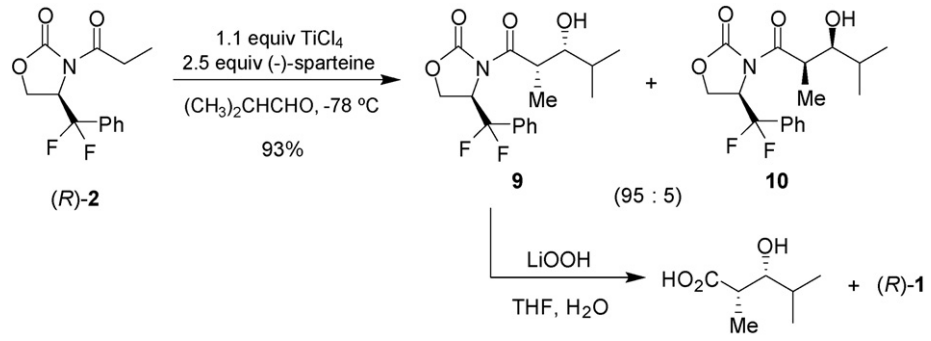
2. Results and discussion

Following the procedure described by Uneyama et al. [8], we first prepared the starting imidoyl chloride **3** in 97% yield from α,α-difluorophenylacetic acid. This acid, in turn, had been prepared with the aid of procedures described in the literature, albeit with slight modifications in the fluorination of the commercially available α-ketoester and subsequent hydrolysis of the resulting ester [9,10]. Sulfoxide **4** was prepared in accordance with the methodology described by Alcudia and coworkers, in which the reaction of diacetonide-D-glucose with dimethyl sulfinyl chloride followed by treatment with 1-naphthylmagnesium bromide affords the enantiomerically pure compound **4** [11] (Scheme 2). The β-imino sulfoxide **5** was obtained from the reaction of **3** and **4** in 89% yield [12]. The diastereoselective reduction of the imine to an amine group was achieved by employing $NaBH_4$ in a THF/MeOH solvent mixture at −40 °C to afford the β-aminosulfoxide **6** with a *syn*:*anti*-dr of 95:5 and in 91% yield [13]. Enantiopure *syn*-**6** was obtained after



(a) LDA (2 equiv), THF, -78 ºC. (b) $NaBH_4$ (4 equiv) THF/MeOH (2:1), -40 ºC. (c) CAN, CH_3CN/H_2O,rt, (78%). (d) $ClCO_2Bn$, dioxane/aq K_2CO_3 50%, rt, (92%). (e) (i) TFAA, CH_3CN, *sym*-collidine, 0 ºC; (ii) K_2CO_3 (10%); (iii) $NaBH_4$, H_2O, (three steps, 79%). (f) NaH(1.5 equiv), DMF, 0 ºC, (88%). (g) (i) NaH (1.5 equiv), DMF, 0 ºC; (ii) propionyl chloride (1.5 equiv), 0 ºC, (87%).

Scheme 2. Synthesis of fluorinated *N*-acyloxazolidinone (*R*)-**2**.



Scheme 3.

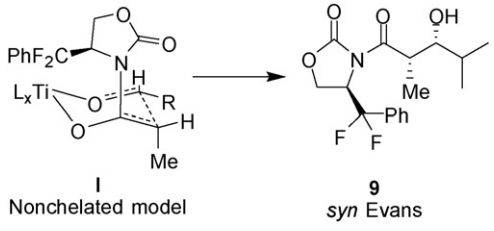
Table 1
Aldol condensation of (*R*)-**2** with isobutyraldehyde for the selective preparation of the *syn*-non-Evans addition product

Entry	$TiCl_4$[a]	DIPEA[b]	Me_2CHCHO[c]	*T* (°C)[d]	Yield (%)[e]	**10**:**9**:*anti*[f]
1	2	1.1	1.1	−78	28	48:18:13:21
2	4	2.2	4.4	−78	78	66:21:11:2
3	8	4.4	4.4	−78	79	86:10:4:0
4	8	4.4	8.8	−78	83	93:3:4:0
5	2	1.1	1.1	0	54	67:22:6:5
6	4	2.2	2.2	0	70	79:10:7:4

[a] Equivalents of $TiCl_4$.
[b] Equivalents of $(i\text{-Pr})_2EtN$.
[c] Equivalents of Me_2CHCHO.
[d] Temperature for aldehyde addition and subsequent reaction.
[e] Total yield of all diastereoisomers.
[f] Ratio of diastereoisomers determined by means of ^{19}F NMR and HPLC-MS.

purification by means of flash chromatography. The next step was the replacement of the 1-naphthylsulfinyl auxiliary with a hydroxyl group. With this goal in mind, the PMP group of *syn*-**6** was oxidatively cleaved (CAN, 5 equiv.) and the amino group was reprotected with $ClCO_2Bn$. The ''non-oxidative'' Pummerer reaction (NOPR) of the Cbz-protected aminosulfoxide **7** furnished *N*-Cbz protected aminoalcohol **8** in good yield [14]. Treatment of **8** with NaH in DMF led to an intramolecular cyclization, thus providing the enantiomerically pure fluorinated oxazolidinone (*R*)-**1** in a yield of 88%. Oxazolidinone (*R*)-**1** was readily acylated by treatment with NaH and propionyl chloride in DMF at 0 °C to provide (*R*)-**2** as a crystalline white solid in 87% yield (Scheme 2).

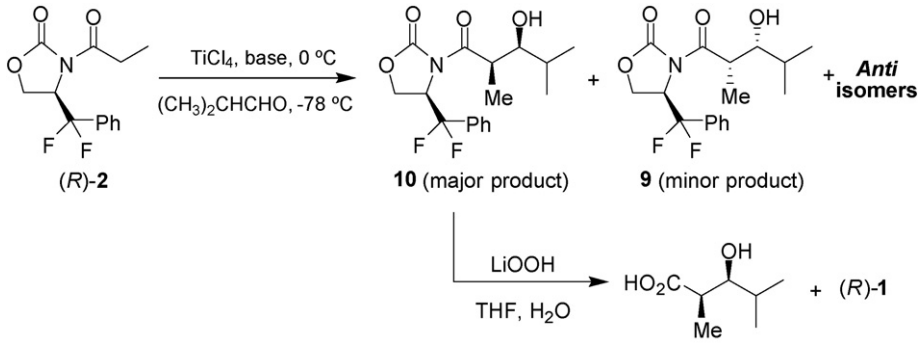
After obtaining fluorinated *N*-acyloxazolidinone (*R*)-**2**, we decided to test its reactivity with isobutyraldehyde under the conditions previously described by Crimmins et al. [15]. Initially, we applied the conditions necessary for obtaining the *syn*-Evans addition product by treating (*R*)-**2** with 1.1 equiv. $TiCl_4$ and 2.5 equiv. of (−)-sparteine at 0 °C, followed by slow addition of 1.1 equiv. of isobutyraldehyde at −78 °C. The Aldol reaction was complete after 5 min with a diastereoselectivity ratio of 95:5 *syn*-Evans **9**/*syn*-non-Evans **10** and a yield of 93% (Scheme 3) [16]. No detectable amount of the two *anti*-products was observed. While this result is comparable in terms of selectivity to that previously obtained by Crimmins, our reaction produced a much higher chemical yield (93% in contrast to 70% under the same conditions). In order to determine the structure of the predominant diastereoisomer **9**, it was first isolated by means of flash chromatography and then the chiral auxiliary was removed through hydrolysis with LiOOH in THF/H_2O to afford the corresponding carboxylic acid. After comparing the NMR and specific rotation data of this compound to those described in the literature [17], we proposed the configuration depicted in Scheme 3 as the absolute configuration of **9**. (*R*)-**1** was recovered in 88% yield from the hydrolysis reaction.



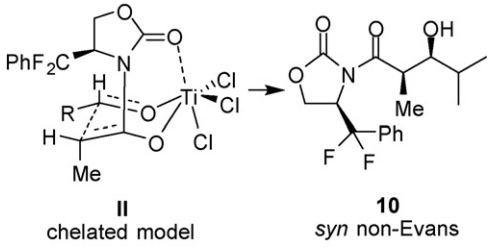
Scheme 4.

The formation of this diastereoisomer can be explained by invoking a non-chelated transition state **I**, which has been previously proposed for the boron enolate of *N*-acyloxazolidinones [18]. In this model, the metal center is coordinated to (−)-sparteine in the transition state, which prevents the metal from coordinating to the carbonyl oxygen of the oxazolidinone ring, thus leading to the *syn*-Evans addition product (Scheme 4).

Next, we decided to perform the same reaction under the conditions previously described for the selective preparation of



Scheme 5.



Scheme 6.

the *syn*-non-Evans diastereoisomer [15]. In this case, the formation of the enolate of (*R*)-**2** is achieved through the addition of 2.0 equiv. of $TiCl_4$ and 1.1 equiv. of (−)-sparteine at 0 °C, followed by slow addition of 1.1 equiv. of isobutyraldehyde at −78 °C. Although the reaction was kept at −78 °C for 2 h, it did not progress further and a large amount of starting material remained unreacted. The analysis of the crude reaction mixture revealed the presence of a diastereoisomeric mixture *syn*-non-Evans (**10**)/*syn*-Evans (**9**)/*anti* in a ratio of 70:24:6 [19], but the total yield for all the diastereoisomers was only 24%. As was the case with compound **9**, the major diastereoisomer **10** was purified by means of flash chromatography and then the chiral auxiliary was removed through hydrolysis with LiOOH in THF/H_2O. The carboxylic acid thus obtained was identified through comparison of its NMR and specific rotation data with those previously reported [17].

In order to improve both the yield and diastereoselectivity for the *syn*-non-Evans addition product, we decided to optimize the reaction conditions and to use diisopropyl ethyl amine (DIPEA) instead of the more costly (−)-sparteine. These changes led to more satisfactory results for this transformation (Table 1 and Scheme 5).

From the results shown in the table it is obvious that the major diastereoisomer is always the *syn*-non-Evans Aldol product **10** and that a significant improvement in both the chemical yield and diastereoselectivity is achieved when an excess of the aldehyde is added, which is in agreement with previously reported results for non-fluorinated analogs [20]. Interestingly, while an increase of the temperature from −78 to 0 °C causes the yield to increase, the reaction becomes less diastereoselective, with the formation of unidentified side products.

The formation of the *syn*-non-Evans diastereoisomer **10** can be explained with a chelated transition state **II** (Scheme 6). In this case, the base is in deficiency relative to the titanium; thus, the metal can coordinate to both the carbonyl oxygen of the oxazolidinone and the aldehyde to furnish the *syn*-non-Evans **10** addition product [13,21].

3. Conclusions

In summary, the enantioselective synthesis of a new fluorinated chiral oxazolidinone has been achieved. The preliminary studies of its reactivity as a chiral auxiliary in Aldol reactions show that it is effective for the preparation of the desired products, with yields and diastereoselectivities comparable or better than those found in related non-fluorinated systems previously described in the literature. Further studies concerning its use as a chiral auxiliary in other reactions are under way in our laboratories.

4. Experimental

4.1. General experimental procedures

All reactions were performed with magnetic stirring in flame-dried glassware under an argon atmosphere with dry, distilled solvents. Tetrahydrofuran (THF) was distilled over Na–K alloy. Dichloromethane (CH_2Cl_2) was distilled over CaH_2. Acetonitrile (CH_3CN) was distilled over P_2O_5 and collected under inert atmosphere over molecular sieves (4 Å). All other commercially obtained solvents or reagents were used as received. All reactions were monitored with thin layer chromatography (TLC) in which precoated 250 μm softlayer silica gel GF uniplates (Merck) were used. TLC plates were visualized with UV light (254 nm), vanillin, or cerium molybdate stains. Flash chromatography was performed with the indicated solvent system on 60 (230–400 mesh, particle size 0.040–0.063 mm) normal phase silica gel. In several cases, all of which are clearly identified in the text, the silica gel for column chromatography was deactivated prior to the actual separation through overnight treatment with a 2% solution of triethylamine in hexane, followed by equilibration with the solvent mixture finally employed. 'Concentrated' refers to the removal of solvent with a rotary evaporator at normal water

aspirator pressure followed by further evacuation with a two-stage mechanical pump. Yields refer to chromatographically and spectroscopically pure compounds. All new compounds were determined to be at least 95% pure by means of NMR. All melting points were determined with an open capillary. Chemical shifts were reported in δ values relative to tetramethylsilane in ^{1}H NMR standard, fluorotrichloromethane in ^{19}F NMR, and the solvent peak in ^{13}C NMR. ^{1}H NMR was measured at 300 MHz, ^{19}F NMR at 282.4 MHz, and ^{13}C NMR at 75.5 MHz. The units for coupling constants are Hertz (Hz). Peak splitting patterns in NMR are reported as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

4.1.1. 2,2-Difluoro-N-(4-methoxyphenyl)-2-phenylacetimidoyl chloride (**3**)

This compound was prepared in accordance with the protocol previously described [8], starting from the corresponding acid. Purification by means of distillation under reduced pressure (b.p. 102 °C at 6×10^{-2} Torr) gave a yellow oil (97%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.67 (s, 3H), 6.79 (d, $J = 9.1$, 2H), 7.01 (d, $J = 9.0$, 2H), 7.35–7.58 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 55.8 (c), 114.5 (d), 116.0 (t, $^{1}J_{CF} = 249$), 123.3 (d), 126.4 (t, $^{3}J_{CF} = 5.7$), 128.9 (d), 131.2 (d), 133.9 (t, $^{2}J_{CF} = 26.4$), 137.5 (s), 137.9 (t, $^{2}J_{CF} = 37.0$), 158.9 (s); ^{19}F NMR ($CDCl_3$, 282.4 MHz) δ (ppm): −97.0 (s, 2F). HRMS Calc. for $C_{15}H_{12}ClF_2NO$: 295.0575, Found: 295.0586.

4.1.2. (+)-(S_S)-3,3-Difluoro-3-phenyl-N-(p-methoxyphenyl)-2-iminopropyl-1-(1-naphtyl)sulfoxide (**5**)

This compound was prepared in accordance with the protocol previously described [12], starting from **3** and **4**. Purification by means of flash chromatography (*n*-hexane-EtOAc (2:1)) on deactivated silica gel ($R_f = 0.3$) afforded a white solid (89% yield): m.p. 124–126 °C; $[\alpha]_D^{25}$: +29.4° (*c* 1.05; $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.73 (s, 3H), 3.92 (d, $J = 12.8$, 1H), 3.97 (d, $J = 12.7$, 1H), 6.78 (s, 4H), 7.41–7.99 (m, 12H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 54.8 (t), 55.8 (c), 114.6 (d), 114.6 (d), 118.8 (t, $^{1}J_{CF} = 246$), 121.4 (d), 121.8 (d), 123.2 (d), 126.1 (d), 126.7 (t, $^{3}J_{CF} = 6.0$), 127.3 (d), 128.0 (d), 128.2 (d), 128.9 (d), 129.0 (d), 129.4 (d), 130.9 (s), 132.2 (d), 133.8 (s), 134.5 (t, $^{2}J_{CF} = 25.9$), 140.3 (s), 140.8 (s), 157.8 (s), 158.1 (t, $^{2}J_{CF} = 33.0$); ^{19}F NMR ($CDCl_3$, 282.4 MHz) δ (ppm): −95.92 (d, $J = 283$, 1F), −97.07 (d, $J = 283$, 1F). HRMS Calc. for $C_{26}H_{21}F_2NO_2S$: 450.1339, Found: 450.1349.

4.1.3. (−)-(2S,S_S)-3,3-Difluoro-3-phenyl-N-(p-methoxyphenyl)-2-aminopropyl-1-(1-naphtyl)sulfoxide (syn-**6**)

To a stirred solution of β-imino sulfoxide **5** (6.7 mmol) in 50 mL of THF/MeOH (2:1) at −40 °C, an excess of $NaBH_4$ (1.1 g, 26.8 mmol) was added portion-wise, after which the temperature was allowed to rise to −20 °C. The mixture was then stirred for 5 h until the starting material **5** totally disappeared, as determined through TLC analysis. After quenching the reaction with saturated aqueous NH_4Cl, the organic layer was separated and the aqueous phases extracted with dichloromethane (3×20 mL). The combined organic extracts were washed with brine (3×20 mL), dried (Na_2SO_4), and concentrated *in vacuo* to furnish a yellowish solid containing a mixture of diastereoisomers. Medium pressure liquid chromatography (MPLC) [*n*-hexane/EtOAc (5:1)] on deactivated silica gel ($R_f = 0.2$) provided the diastereomerically pure *syn*-**6** as a white crystalline solid (91%). m.p. 97–99 °C; $[\alpha]_D^{25}$: −251.8° (*c* 1.00; $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 2.90 (dd, $J_1 = 13.7$, $J_2 = 7.0$, 1H), 3.45 (dd, $J_1 = 13.8$, $J_2 = 5.9$, 1H), 3.64 (s, 3H), 4.36–4.47 (m, 1H), 6.37 (d, $J = 8.9$, 2H), 6.61 (d, $J = 9.0$, 2H), 7.29–7.50 (m, 8H), 7.76–7.93 (m, 4H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 54.5 (t, $^{2}J_{CF} = 30.2$), 54.6 (c), 55.5 (t), 113.6 (d), 114.0 (d), 120.4 (d), 120.9 (t, $^{1}J_{CF} = 249$), 122.1 (d), 124.6 (d), 124.8 (t, $^{3}J_{CF} = 6.3$), 125.7 (d), 126.4 (d), 127.4 (d), 127.5 (s), 128.0 (d), 129.4 (d), 130.3 (d), 132.4 (s), 132.9 (t, $^{2}J_{CF} = 25.9$), 138.2 (s), 138.3 (s), 151.8 (s); ^{19}F NMR ($CDCl_3$, 282.4 MHz) δ (ppm): −100.8 (dd, $^{1}J_{FF} = 250$, $^{2}J_{FH} = 8.2$, 1F), −107.2 (dd, $^{1}J_{FF} = 249$, $^{2}J_{FH} = 12.4$, 1F). HRMS Calc. for $C_{26}H_{23}F_2NO_2S$: 451.1418, Found: 451.1410.

4.1.4. (−)-(2S,S_S)-2-(N-Benzyloxycarbonyl)aminopropyl-3,3-difluoro-3-phenyl-1-(1-naphtyl)sulfoxide (syn-**7**)

This compound was prepared in accordance with a previously described protocol [13] with **6** as a starting compound. Purification by means of flash chromatography (*n*-hexane-EtOAc (2:1)) on deactivated silica gel ($R_f = 0.4$) gave a white solid (72%): m.p. 137–139 °C; $[\alpha]_D^{25}$: −181.4° (*c* 1.00; $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.17 (s, 1H), 2.97 (dd, $J_1 = 14.1$, $J_2 = 9.6$, 1H), 3.45 (dd, $J_1 = 14.1$, $J_2 = 3.4$, 1H), 4.78–4.91 (m, 3H), 7.08 (m, 13H), 7.78–8.01 (m, 4H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 50.8 (t, $^{2}J_{CF} = 30.6$), 53.7 (t), 66.0 (t), 119.9 (t, $^{1}J_{CF} = 249$), 120.3 (d), 122.7 (d), 124.5 (d), 124.5 (d), 124.6 (d), 124.7 (d), 125.7 (d), 126.5 (d), 126.9 (d), 127.1 (d), 127.4 (d), 128.1 (d), 129.4 (s), 130.5 (s), 132.4 (s), 134.9 (s), 137.1 (s), 154.1 (s); ^{19}F NMR ($CDCl_3$, 282.4 MHz) δ (ppm): −104.3 (dd, $^{1}J_{FF} = 249$, $^{2}J_{FH} = 9.3$, 1F), −107.4 (dd, $^{1}J_{FF} = 247$, $^{2}J_{FH} = 14.4$, 1F). HRMS Calc. for $C_{27}H_{23}NO_3F_2S$: 479.1367, Found: 479.1350.

4.1.5. (−)-(2R)-2-(N-Benzyloxycarbonyl)amino-3,3-difluoro-3-phenylpropanol (**8**)

This compound was prepared in accordance with a previously described protocol [13], starting from **7**. Purification by flash chromatography (*n*-hexane-EtOAc (3:1)) on deactivated silica gel ($R_f = 0.25$) gave a white solid (79%): m.p. 93–95 °C; $[\alpha]_D^{25}$: −20.1° (*c* 1.03; $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 2.49 (t, $J = 6.4$, 1H), 3.53–3.58 (m, 2H), 4.18–4.21 (m, 1H), 4.77 (d, $J = 12.2$, 1H), 4.86 (d, $J = 12.2$, 1H), 5.40 (d, $J = 9.8$, 1H),7.10–7.29 (m, 10H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 58.0 (t, $^{2}J_{CF} = 27.6$), 60.6 (t), 67.6 (t), 121.8 (t, $^{1}J_{CF} = 248$), 125.8 (t, $^{3}J_{CF} = 6.3$), 128.4 (d), 128.6 (d), 128.9 (d), 130.7 (d), 134.8 (t, $^{2}J_{CF} = 25.6$), 136.4 (s), 156.9 (s); ^{19}F NMR ($CDCl_3$, 282.4 MHz) δ (ppm): −103.9 (dd, $^{1}J_{FF} = 249$, $^{2}J_{FH} = 14.4$, 1F), −105.2 (dd, $^{1}J_{FF} = 251$,

$^2J_{FH}$ = 12.4, 1F). HRMS Calc. for $C_{17}H_{17}NO_3F_2$: 321.1176, Found: 321.1180.

4.1.6. (−)-(4R)-4-(Phenyldifluoromethyl)-oxazolidin-2-one (1)

To a stirred solution of amino alcohol **8** (0.5 g, 1.56 mmol) in 8 mL of DMF at 0 °C, NaH (0.056 g, 2.33 mmol) was added portion-wise. The mixture was then stirred for 30 min until the starting material **8** totally disappeared, as determined through TLC analysis. The solvent was removed under reduced pressure and the solid residue was redissolved in water (10 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to afford the crude reaction product, which was purified by means of flash chromatography (*n*-hexane-EtOAc (2:1)) on silica gel (R_f = 0.15) to afford a white solid (91% yield). m.p. 76–78 °C; $[\alpha]_D^{25}$: −9.7° (*c* 1.00; $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 4.17–4.40 (m, 3H), 6.76 (s, 1H), 7.40 (s, 5H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 56.5 (t, $^2J_{CF}$ = 32.8), 63.5 (t), 118.7 (t, $^1J_{CF}$ = 247), 124.5 (t, $^3J_{CF}$ = 6.3), 127.9 (d), 130.0 (d), 131.4 (t, $^2J_{CF}$ = 25.6), 158.4 (s); ^{19}F NMR ($CDCl_3$, 282.4 MHz) δ (ppm): −109.8 (dd, $^1J_{FF}$ = 252, $^2J_{FH}$ = 9.3, 1F), −110.8 (dd, $^1J_{FF}$ = 252, $^2J_{FH}$ = 10.3, 1F). HRMS Calc. for $C_{10}H_9NO_2F_2$: 213.0601, Found: 213.0599.

4.1.7. (−)-(4R)-4-(Phenyldifluoromethyl)-3-propionyl-oxazolidin-2-one (2)

NaH (0.025 g, 1.05 mmol) was added portion-wise to a stirred solution of oxazolidinone **1** (0.15 g, 0.7 mmol) in 8 mL of DMF at 0 °C. After stirring for 20 min, propionyl chloride (0.092 mL, 1.05 mmol) was added drop-wise and the mixture was allowed to react for 1 h. The solvent was evaporated under reduced pressure and the solid residue was redissolved in water (10 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to afford a yellow oil as crude reaction product. The purification was carried out by means of flash chromatography (*n*-hexane-EtOAc (1:2)) on silica gel (R_f = 0.8) to afford a white solid (87%): m.p. 76–78 °C; $[\alpha]_D^{25}$: −8.98° (*c* 1.00; $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.98 (t, *J* = 7.4, 3H), 2.75–2.83 (m, 2H), 4.24 (dd, J_1 = 9.4, J_2 = 8.9, 1H), 4.47 (dd, J_1 = 9.8, J_2 = 1.5, 1H), 5.06 (dd, J_1 = 18.8, J_2 = 10.5, 1H), 7.40 (s, 5H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 7.3 (c), 27.9 (t), 56.4 (t, $^2J_{CF}$ = 37.2), 62.1 (t, $^3J_{CF}$ = 6.9), 119.1 (t, $^1J_{CF}$ = 250), 124.5 (t, $^3J_{CF}$ = 3.2), 127.7 (d), 127.7 (d), 129.9 (d), 131.7 (t, $^2J_{CF}$ = 25.3), 152.3 (s), 171.9 (s); ^{19}F NMR ($CDCl_3$, 282.4 MHz) δ (ppm): −107.9 (dd, $^1J_{FF}$ = 252, $^2J_{FH}$ = 11.3, 1F), −110.1 (dd, $^1J_{FF}$ = 252, $^2J_{FH}$ = 11.3, 1F). HRMS Calc. for $C_{13}H_{13}NO_3F_2$: 269.0863, Found: 269.0867.

4.1.8. General procedure for the preparation of the syn-Evans addition product, (4R)-4-(phenyldifluoromethyl)-N-(2S,3R)-(3-hydroxy-2,4-dimethyl-1-pentanoyl)-1,3-oxazolidin-2-one (9)

To a round-bottom flask containing oxazolidinone **2** (0.19 mmol) in CH_2Cl_2 (2 mL) under argon atmosphere at 0 °C, $TiCl_4$ (0.21 mmol, 1 M in CH_2Cl_2) was added and stirred for 5 min at that temperature. (−)-Sparteine (0.47 mmol) was then carefully added drop-wise to the resulting yellow mixture, which changed color to red, thus indicating the formation of the enolate. After 30 min at 0 °C, the reaction was cooled to −78 °C, the corresponding aldehyde (0.21 mmol) was added slowly, and the mixture was stirred for 5 min, after which the starting material disappeared (TLC). The reaction was quenched with a saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2 (3 × 3 mL). The organic phases were pooled together, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification by means of flash chromatography [*n*-hexane-EtOAc (1:2)] on silica gel afforded pure compound **9** as a colorless viscous oil (89% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.77 (d, *J* = 6.8, 3H), 0.91 (d, *J* = 6.6, 3H), 1.07 (d, *J* = 7.1, 3H), 1.50–1.62 (m, 1H), 2.16 (broad s, 1H), 3.34 (dd, J_1 = 8.8, J_2 = 2.5, 1H), 3.70–3.78 (m, 1H), 4.26–4.32 (m, 1H), 4.55 (dd, J_1 = 9.8, J_2 = 1.7, 1H), 5.05–5.16 (m, 1H), 7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 9.4, 17.7, 18.3, 29.3, 38.7, 56.2 (t, $^2J_{CF}$ = 32.4), 62.0 (t, $^3J_{CF}$ = 3.7), 74.9, 118.9 (t, $^1J_{CF}$ = 250), 124.6 (t, $^3J_{CF}$ = 6.3), 127.7, 130.0, 131.4 (t, $^2J_{CF}$ = 25.3), 151.5, 175.9; ^{19}F NMR ($CDCl_3$, 282.4 MHz) δ −108.3 (dd, $^1J_{FF}$ = 254, $^2J_{FH}$ = 10.3, 1F), −110.4 (dd, $^1J_{FF}$ = 253, $^2J_{FH}$ = 12.4, 1F); MS (EI) Calc. for ($M - H_2O$) $C_{17}H_{19}F_2NO_3$: 324.14, Found: 324.10.

4.1.9. General procedure for the preparation of the syn-non-Evans addition product, (4R)-4-(phenyldifluoromethyl)-N-(2R,3S)-(3-hydroxy-2,4-dimethyl-1-pentanoyl)-1,3-oxazolidin-2-one (10)

To a round-bottom flask containing the oxazolidinone **2** (50 mg, 0.19 mmol) in CH_2Cl_2 (2 mL) under argon atmosphere at 0 °C, $TiCl_4$ (1.52 mmol, 1 M in CH_2Cl_2) was added and stirred for 5 min at that temperature. Diisopropylethylamine (0.142 mL, 0.84 mmol) was then slowly added drop-wise to the resulting yellow mixture. After 30 min at 0 °C, the reaction was cooled to −78 °C and isobutyraldehyde (121 mg, 1.68 mmol) was slowly added. This mixture was then stirred until TLC analysis indicates that there was no more starting material. The reaction mixture was then quenched with a saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2 (3 × 3 mL). The organic phases were pooled together, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification by means of flash chromatography [*n*-hexane-EtOAc (1:2)] afforded pure compound **10** as colorless viscous oil (77% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.85 (d, *J* = 6.8, 3H), 0.94 (d, *J* = 6.6, 3H), 1.01 (d, *J* = 6.6, 3H), 1.52–1.59 (m, 1H), 1.80 (br s, 1H), 3.34 (dd, J_1 = 8.3, J_2 = 2.8, 1H), 3.86–3.94 (m, 1H), 4.22–4.28 (m, 1H), 4.48 (dd, J_1 = 9.8, J_2 = 1.7, 1H), 5.08–5.19 (m, 1H), 7.40–7.45 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 8.9, 15.4, 15.8, 22.1, 57.1 (t, $^2J_{CF}$ = 34.5), 61.9, 62.7 (t, $^3J_{CF}$ = 6.7), 118.2 (t, $^1J_{CF}$ = 248), 124.7 (t, $^3J_{CF}$ = 3.4), 127.8, 127.9, 129.6, 132.0 (t, $^2J_{CF}$ = 26.3), 154.7, 171.0; ^{19}F NMR ($CDCl_3$, 282.4 MHz) δ −107.5 (dd, $^1J_{FF}$ = 252, $^2J_{FH}$ = 10.3, 1F), −109.4 (dd, $^1J_{FF}$ = 253, $^2J_{FH}$ = 12.3, 1F); MS (EI) Calc. for ($M - H_2O$) $C_{17}H_{19}F_2NO_3$: 324.14, Found: 324.10.

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